AMERICAN JOURNAL OF PHARMACY

and

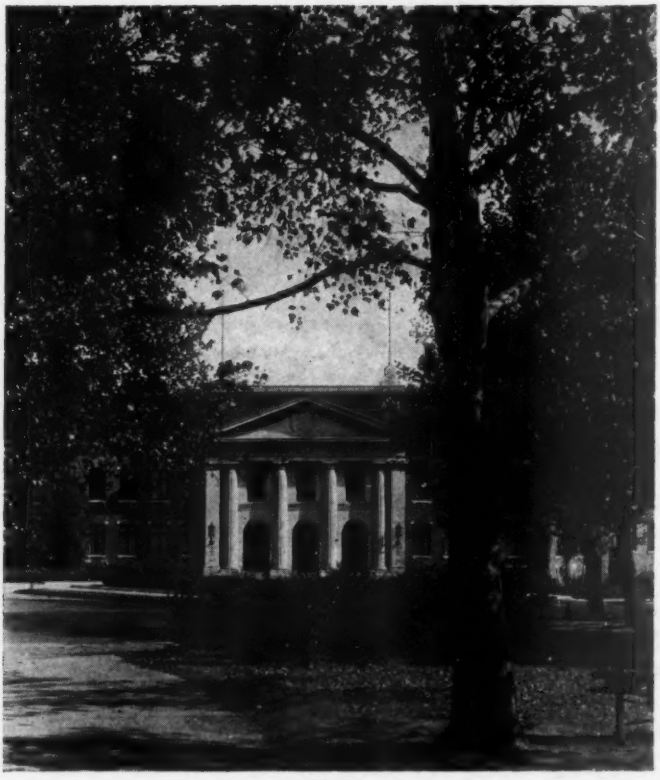
THE SCIENCES SUPPORTING PUBLIC HEALTH

SINCE 1825

DR. JULIUS W. STURMER

(see p. 234)

JULY
1943



PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

43rd Street, Kingsessing and Woodland Avenues

PHILADELPHIA 4, PENNSYLVANIA

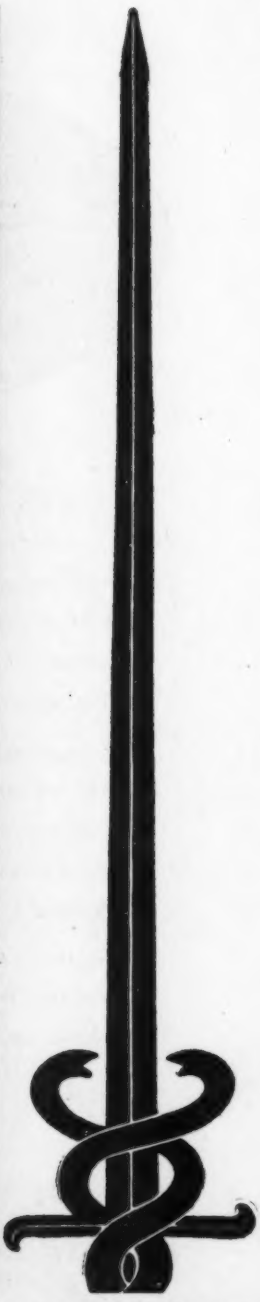
Founded 1821

ENLIST TODAY in the fight AGAINST CANCER

160,000 Americans die of cancer annually. Authorities say *many of these deaths could be avoided.*

Help us spread the knowledge that *cancer can, in many cases, be cured.* Enlist today in your local unit of the Women's Field Army.

In the Metropolitan Area, address the
New York City Cancer Committee
130 East 66th Street



ERICAN SOCIETY FOR THE CONTROL OF CANCER

350 MADISON AVENUE, NEW YORK CITY

New WINTHROP PRODUCTS *for increased professional volume*

The sale of professional products is the most important phase of pharmacy. New Winthrop preparations supply volume items to balance the declining availability of sundries.

Our large sales force and national advertising will bring the new products to the immediate attention of prescribing physicians.

Order these products from your wholesaler. Then tell doctors that you have them in stock.

ACIDOL CAPSULES of 4 gr.
Bottles of 50

DIETHYLSTILBESTROL DIPROPIONATE
Tablets (enteric coated) and Ampuls in Oil

PHENARSINE HYDROCHLORIDE
Ampuls of 0.045 Gm.
(supplied with or without water)
Ampuls of 0.068 Gm.
(supplied with or without water)
Ampuls of 0.45 Gm.
Ampuls of 0.68 Gm.

PONTOCAINE HYDROCHLORIDE "NIPHANOID"
for Continuous Caudal Analgesia
Ampuls of 250 mg.

SULFATHIAZOLE OINTMENT
Tubes of 1 ounce

SULFATHIAZOLE EYE OINTMENT
Tubes of 1/8 ounce

SULFATHIAZOLE—UREA OINTMENT
Tubes of 1 ounce

AFAXIN CAPSULES, 50,000 Units
Boxes of 25 and 100

BETASYNPLEX
Ampuls (instantly soluble "Niphanoid" form)
Tablets (Plain or with Iron)

BETASYNPLEX ELIXIR
(Plain or with Iron)

Winthrop
WINTHROP

CHEMICAL COMPANY, INC.
Pharmaceuticals of merit for the physician
170 VARICK STREET, NEW YORK 13, N. Y.

AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

Vol. 115. JULY, 1943 No. 7

CONTENTS

Published monthly by the Philadelphia College of Pharmacy and Science 43rd Street, Kingsessing and Woodland Avenues, Philadelphia, Pa.

Annual Subscription, $3.00 **Foreign Postage, 25 Cents Extra**
Single Numbers, 30 Cents **Back Numbers, 50 Cents**

Entered as Second-Class Matter at the Post Office at Philadelphia, Pa. Under Act of March 3, 1879

Acceptance for Mailing at Special Rate of Postage Provided for in Section 1103 Act of October 3, 1917. Authorized February 15, 1920

OUR COVER

WE dedicate this month's issue of the JOURNAL to one who has long served pharmacy and the allied professions as teacher, author and friend.

Dr. Sturmer graduated from Purdue University in 1891 and was a member of its faculty until 1912 when he moved east to become Professor and Dean of Pharmacy at the Medico-Chirurgical College of Philadelphia. In 1916 "Medico-Chi" was merged with the University of Pennsylvania which latter institution entered into an agreement with the Philadelphia College of Pharmacy transferring its pharmacy students there. Here Dr. Sturmer became Professor of Pharmaceutical Chemistry and later Dean of Science in which position he served for many years.

Dr. Sturmer was awarded many academic degrees, receiving the Doctor of Pharmacy, the Master of Pharmacy and the Doctor of Science. Throughout his long period of service he was a diligent worker in developing pharmaceutical education to its present stature. He was long active in the American Association of Colleges of Pharmacy and served as its president in 1930-31.

Dr. Sturmer was a key figure in the expansion of the activities of the Philadelphia College of Pharmacy in such wise as to provide standard curricula in the fields of Chemistry, Bacteriology and Biology and this led to a change in the name of this institution to The Philadelphia College of Pharmacy & Science in 1921.

Dean Sturmer was the editor of standard texts in both Pharmaceutical Latin and Arithmetic and also contributed in many other ways to the scientific literature.

On July 1st, Dr. Sturmer announced his retirement as Dean after 42 years of academic life. His affiliation with the college as a member of the Board of Trustees continues as does his membership on the Publication Committee of this JOURNAL. We join his host of friends, the country over, in wishing him the joy and serenity that comes only to those who can look with quiet satisfaction to a long period of service in behalf of their chosen field.

Those of us who were affiliated with him closely will miss his quiet judgment tempered by years of experience and observation.

EDITORIAL

INTRAVENOUS THERAPEUTIC FLUIDS *

THE treatment of pathologic states affecting interchange of body fluids demands something more than generalizations. Such a course may lead to very grave danger. It is conceivable that battle conditions may alter the circumstantial aspects of the problem, but basically the approach should have intelligent understanding.

To crowd the circulating blood stream with additional fluid purely because it is at hand has often led to irreparable error. There was a time when salt and dextrose answered by rote every surgical intravenous replacement need, a circumstance that not infrequently produced edema and drowning of the patient in his own fluid. Due to the pioneering work of Hartman, Maddock, Coller, Wangensteen, and others, a more rational approach to this subject has come to the fore. The physiology of body fluids has taken on an intelligible aspect, exacting a knowledge that dissipates vagueness in the therapeutic application of these agents. In the light of recent investigations, intravenous fluids demand individual consideration.

Replacement of normal constituents of the blood presupposes cognizance of an imbalance occasioned by depletion of water, minerals, salts, protein, glucose, red and white blood cells, and platelets, fundamentals of the circulating blood stream. Feeding the patient intravenously to maintain food and fluid balance also involves consideration of vitamin therapy and other specifically indicated substances.

Drugs, bacteria, protein products, and the like may categorize the abnormal constituents of the blood—assuredly existent at times to the great disadvantage of the patient.

To the trilogy of modern therapy, morphine, sulfonamide, and plasma, may be attributable the decreased mortality in war casualties. Men have been known to go into battle, heartened with the knowledge that plasma was available to combat their wounds. Plasma, however, is not a blood substitute. It is a blood derivative and as such has its limitations even as have the other members of the triad.

*Reprinted from *U. S. Naval Med. Bull.*, July, 1943.

There are circumstances when whole blood, and whole blood alone, must take precedence. In severe hemorrhage wherein the oxygen-carrying capacity of the blood is depleted and anoxia is present, replacement therapy demands supplying the medium of oxygen conveyance. Where there is anoxemia there is continued permeability, and the loss of fluid will be unchecked by any other substitute. Anemia, purpura, and monoxide poison, among others, are likewise definite indications for whole blood. Replacement by any other substitute attenuates the logic of this type of therapy.

Burns, shock, severe hypoproteinemia from liver disease, and the nephrotic syndrome are clear indications for the use of plasma. The maintenance of proper hydrostatic pressure within the capillary bed and the replacement of plasma protein in sufficient amounts by whole blood under these conditions may lead to severe overconcentration of red cells, increase viscosity, produce circulatory resistance, and overburden the heart.

In these circumstances, and in the prevention of shock, plasma is adequate. Its availability in quantity, general lack of unfavorable reaction, and pooling have entrenched this derivative as a therapeutic essential. Although perhaps physiologically less ideal than whole blood, its positive success has astounded conservative opinion.

Serum and the albumin fraction of the blood, on the other hand, demand more careful consideration, as their use is decidedly restricted. Serum as such has not been accepted as a blood substitute by the armed services.

Albumin, however, is of value in traumatic shock, burns, and hypoproteinemia. It is not a substitute for plasma, much less for whole blood. Its principal effectiveness is in reestablishment and maintenance of the colloid osmotic pressure of the blood. It increases blood volume but at the expense of the tissue fluids, and hence in the presence of dehydration requires complemental fluids.

In the presence of uncontrolled hemorrhage, serum albumin may increase hemorrhage, aggravate existing dehydration, render worse an apparent anemia, and precipitate pulmonary edema. In traumatic shock, albumin is best limited perhaps to emergency procedures, while in burns it should be followed as soon as possible with citrated plasma.

Conversely the intravenous introduction of a diffusible crystalloid such as salt or dextrose to a patient in deep shock or dehydration may invite catastrophe. Such a procedure tends to wash out

the plasma protein, may aggravate a hypoproteinemia to a critical level, and transform an impending state of subhydration to a visible edema.

Surgeons must rely upon a number of guides to determine the intravenous needs of a patient. Hydrostatic pressure, osmotic pressure, and the permeability of the capillaries enter into every intravenous situation. What kind of fluid should be given depends upon the water, electrolyte, blood loss factor, and caloric and nitrogenous requirements of the patient.

A simple circumstance can pyramid one or more of these requirements into an alarming situation. A momentary brisk bleeding, an episode of vomiting, aspiration through an indwelling duodenal tube, air transportation operations, and the like may suddenly dislocate an otherwise equilibrium status and precipitate a crisis.

Finally, selection of substance for fluid replacement presupposes intelligent assessment of involved factors, such as history, environment, available fluid, and physiologic and pathologic influences.

A healthy person presumably possessing a full complement of red cells, blood protein, chlorides, and a general good state of hydration suddenly stricken by disease, war violence, or accident, will require intravenous replacement therapy specifically adapted to the particular need. A severe hemorrhage demands whole blood; shock and its prevention with or without moderate hemorrhage calls for plasma or serum albumin limited to the above mentioned restrictions. Inability to take food or fluids by mouth is offset by the introduction of several liters of salt and/or dextrose solution within 24 hours, the repetition and quantity gaged by certain frequent laboratory determinations. Chronic protracted illness necessitates knowing the mineral supply, hemoglobin concentration, and total plasma protein before instituting intravenous therapy and supplying the deficit with definitive treatment.

The above editorial from a current issue of the U. S. Naval Medical Bulletin is quite timely in view of the current misconception that plasma is the full and complete answer to every possible derangement of the blood supply.—Ed.

CURRENT PROBLEMS RELATING TO VITAMIN AND HORMONE PREPARATIONS *

By Elmer L. Sevringhaus, M. D.**

IT should be realized, of course, that I do not bring to you any sort of suggestions or advice about how to produce these materials, but that I do want to discuss this problem from my point of view.

Now this matter of "point of view" I think could be clarified rather wisely by stating what are the different points of view of which I am aware. There is that of the manufacturer who is interested in the assay business; of the man who is interested in the investigative laboratory; in the clinical laboratory; of the general practicing physician, and of the consuming public. I have had, in my own experience, the point of view of the laboratory investigator and the clinical investigator, because I have had considerable time of my own given to that, tending more and more toward the latter, with very little opportunity to work directly in the laboratory with my own hands in the last few years. My contact with a large number of general practitioners and clinicians extends that point of view vicariously for them. My handling a very considerable clinical service in the hospital helps me to keep in contact with what patients want and with what they need, which is, after all, the most important thing.

I want also to point out that a very happy experience of a little better than 20 years of contact with many of the firms that you represent has helped me to understand, at least in part, the point of view which your firms must maintain, so I shall try to bring together here these different points of view.

There is another point of view in addition to those mentioned: the point of view of the regulatory groups that exist in this country. You understand, even though I may be a member of the Council on Pharmacy and Chemistry, no member of that Council can speak for the Council. Anything I say about regulatory phenomena and activities is purely a matter of statement of what others have recorded or personal opinion of mine.

A second observation I want to make about these different points of view is my personal conviction. It has been substantiated within

*Based on an Address presented before the Scientific Section, American Drug Manufacturers Association, Palmer House, Chicago, Illinois, May 2, 1943.

**University of Wisconsin, Member of the Council on Pharmacy and Chemistry, American Medical Association.

the last few days by published statements from other representatives of the medical profession as well as from the pharmaceutical industry, of the really remarkable and delightful tendency to a mutual confidence in this matter of cooperative endeavor by all of these different agencies that I have just mentioned. In other words, those of us who represent so-called purely scientific investigations must depend on those of you who are on the manufacturing end to produce the material, so that those of us who are on the clinical side can try it out. Thus products become available to those of us on the consuming end. We are getting away from certain aspects of distrust, recognizing that competitive business still exists.

Now with such a point of view, let me try to tackle these two fundamental things, the vitamin and hormone field. The vitamins will be considered first, because with them perhaps more of you are familiar.

Vitamins and Vitamin Products

There is less discussion about some of these matters necessarily than in the case of hormones, because there is better agreement.

The fundamental problem is the individual human requirements. Attempts to define these are at present, from the Drug Administration, a statement of minimum daily need; from the Committee on Food and Nutrition of the National Research Council, a recommendation for a daily allowance of each which is much higher than the minimum need. Then in the forthcoming Supplement to the U. S. P. XII there will be included a definite mixture of vitamins, and the contents of this new hexavitamin capsule—a capsule containing 6 vitamins, which are recognized in the human need, very nearly coincides with the recommended daily allowances of the Food and Drug Nutrition Committee of the National Research Council.

The Food and Drug Administration's statement of minimum amount was adopted earlier than the others. It is relatively inflexible and is not revised either upward or downward until there is convincing evidence and a real consensus to justify those changes. Perhaps it is wise we do have some things that don't change too fast.

Many of us, however, feel that certain parts of the statement of the Food and Drug Administration are too conservative to be in accord with real human needs. There has been no quarrel with the statement in terms of Vitamin A, 4000 units, of D 400 to 800 units.

In the case of thiamine the need is one milligram daily. There has been a tendency of a certain group of clinical investigators to

want to increase that to the neighborhood of two milligrams, or approximately that level, for adults, and to put it in terms of caloric intake. However, there is recent work which is being published, under the exigencies of the need for the military, and for post-war needs of civilian population, which suggests that a higher need for thiamine does not exist; that after all the adult human does not need much more than around one milligram. There is no doubt that the values are somewhat debatable, but the need for thiamine is not tremendous. Perhaps the Food and Drug statement is somewhat nearer the goal toward which we are shooting.

The methods for making such decisions are new and I think you are aware of the difficulties in the assay with animals. In the case of humans it comes down fundamentally to this: How shall we prove that a human needs more thiamine? Is it by finding an excess of thiamine in the urine? Is it by determining thiamine in the blood as compared to an assumed optimum, or by biological tests applied to that human? These questions are unsettled and observations need to be made on blood chemistry, muscle physiology, the status of the entire individual, neuromuscular and psychiatric. It can't be decided in terms of a few days because we know that while thiamine deficiency can be induced in the course of a week or two of deprivation, the real problem is to detect the slight deficiency which may take months to appear. It is an involved problem, and it is impossible to get the final answer now. At least we are settling down to realize that the need for thiamine is of the order of magnitude of one or two milligrams.

Now another one of the problems which come up immediately is what size tablets and injections of thiamine ought to be available for therapy. Is there reason to have everything from a tenth of a milligram to 100 milligrams, in a great variety of tablets, and of ampuls for injection? If that matter could be simplified I believe you folks might have your tasks a little easier, and also not have to provide too many different kinds of units. An effort is under way just at present which I hope will simplify the demands to a smaller number of sizes of pure thiamine.

Now thiamine is one of the easiest things to study. Riboflavin is much more difficult, not only because of its chemical instability, but the lack of decisiveness about the clinical elements. There is still a debate about that. I shall not take time to discuss those evidences until the experimental and clinical investigators can reach clean-cut decisions as to which is riboflavin, which is nicotinic effect, and what

represents a mixture of the two in varying proportions. It will take time, obviously, to work that out. The magnitude of riboflavin need is greater than thiamine, it appears. The suggested need is twice as great, and the order of magnitude suggested by the National Research Council Committee is a little greater.

On nicotinic acid there is fairly good agreement. The order of magnitude is around 20 milligrams a day for an adult, a little more or less with different sizes, and therefore we come to that one-two-ten ratio, which was adopted back in 1941. By agreement between the Food and Drug Administration and the Council on Pharmacy and Chemistry of the American Medical Association, fortification of liver or yeast products with additions of crystalline or synthetic thiamine, riboflavin and nicotinic acid should be in the ratio of one-two-ten, in order to simplify this chaotic mixing of many different things. No attention was given to the rest of the factors in the B complex, because those vitamins are not yet accepted with certainty as human need. I am not saying they are not needed. We do not know that they are. I believe nothing can be set up as definite standards for them.

I feel increasingly that we ought not to be pushing the use of these different factors in the B complex as indispensable nutrients. That ought to be reserved fundamentally for the field of clinical investigation until there is really good evidence on that point. That involves a difference in point of view between the clinical investigator who wants to settle the fact of need, and the manufacturing interest that wants to be the first in the field. How are we going to bring those two together? I am presenting my point of view which is obviously that of a clinician who wants to use the minimum amount of treatment which will accomplish a good result. I believe we ought to be conservative and not be pushing too many of these vitamin shotguns that are at present, of course, on the market.

What about multiple vitamin preparations? There is a field for them. I have belonged to the group which for years has been preaching "get your vitamins from food." That, of course, does not refer to people on the clinically limited diet. I couldn't expect your firms to be entirely in sympathy with that point of view, yet over a long-time point of view I believe you will be. What shall we say, in the face of rationing? What is going to happen with food definitely restricted, less meat available to many of us? The restriction of milk and cream I think is a very strong possibility also, even though there

is no official commitment on that point yet. We face restrictions in butter and oleomargarine and restrictions on the securing of Vitamin D from fish oil, because of the limitation on fishing industries. Most important of all probably is the great limitation in the availability of citrus fruit and tomatoes. I do not have to tell you people about the stringency on ascorbic acid and its distribution. Most of you want more than you can buy at present. I have just published an article appearing in the Wisconsin State Medical Journal, about which some of you know, trying to present a review of that situation with advice to the physicians of the State as to what they can do in such a situation.

Now it is manifestly still possible to buy foods under rationing without getting anybody else's stamps, and get all of the vitamins necessary. It is economically a little more difficult than it used to be. It requires somewhat more wisdom on the part of the purchaser and therefore on the part of the physician who is advising, and a lot of people are increasingly going to take the attitude, "Why worry? Why not buy a multiple vitamin capsule and eat what I please?" Is it possible?

Now the multivitamin and mineral preparations that you people have helped to produce are making available 4,000, usually 5,000 units of A a day, and the government says, "No more" so that puts a very nice uniformity into the picture. I think that out of a dozen products which I recently reviewed two were 4,000 units, all the rest were 5,000, with thiamine in doses varying from one to three, usually very close to two milligrams per daily dose; riboflavin varied somewhat more, from ½ to 3 milligrams per day, usually in the range from 1½ to 3. Nicotinic acid varied from 10 to 30, the 10 representing one type of product, and the 20 or 30 representing another. Ascorbic acid varied most widely, all the way from 10 to 75 milligrams per daily dose, and D, 400 to 800 units, most of them either 500 or 700.

Now you can see with A, D, thiamine, riboflavin, and nicotinic acid there will not be a great deal of debate, but there will be between individual products supplying ascorbic acid in amounts that vary from 10 up to 75 milligrams.

The Food and Drug Administration insists that the standard ascorbic allotment needed for the adult is 30 milligrams, and it challenges any attempt to raise that level by the statement, "Show us the

evidence that scurvy is produced by restricting the level to 30 milligrams." I think that is not the adequate answer to the question. There is much evidence of ascorbic deficiency. If one's ascorbic intake is at about 30 milligrams, it is below the optimum. What is the required intake? That need is still to be defined. My personal impression is based on the most objective evidence with which I have clinical experience, the texture and appearance of the gum. Fundamentally this goes back to the observation that ascorbic deficiency over a long time leads to edema and a retraction of the gum, a separation between the gum and the tooth. We are seeing a reversal of that picture. Restoration of gums which are diseased has been accomplished by doing nothing but adding ascorbic acid to the diet. I am referring to a clinical study we are carrying on, where the ascorbic acid is very low, and we have been able to restore gums by giving ascorbic therapy, and making no other change in the diet. We have changed the dose level back and forth and the dose level which will accomplish the change is not 30 milligrams; it is not 50 milligrams; it is 75 milligrams a day added to the diet. A few had to be given 100 milligrams a day. What does that mean for the human need of ascorbic acid? I think it means it is in the neighborhood of 75, certainly more than 50 milligrams a day, in order to get at the condition of the gums.

Why does it take 100 for some and 75 in others? We have carried out enough correlation to show that more is required in cases with chronic infections such as sinusitis. In pyorrhea there may be a vicious circle; it takes more than the normal amount of ascorbic to overcome the handicap. Therefore I am very much pleased to see in this group interest in a vitamin capsule providing for 6 vitamins, including ascorbic acid, which is an aid if one is trying to provide in one capsule the ordinary adult need. I am sure the Food and Drug Administration requirement of 30 milligrams does not represent an adequate amount and will ultimately have to be revised.

Now when we try to evaluate these different vitamin preparations of which I will speak, I think we ought to evaluate them on perhaps three different standards. The first concerns a multiple vitamin preparation that can be used therapeutically to treat an individual who is grossly deficient in many aspects of the diet. That calls for something very high in concentration or the use of more than one capsule a day.

The second standard is to have in one capsule the entire daily allotment of these different recognized vitamins so one capsule a day will do the job, and if the doctor can get his patient to take one before breakfast, the vitamin question is taken care of for the day.

The third standard, which is probably far the most important, statistically speaking, is to have a vitamin capsule which can be a supplement to the diet. Very few of our patients—and certainly almost none of the public in general, who are not patients—are eating a vitamin-free diet. They would be getting moderate amounts, but questionable amounts, and there I would suggest a product so designed that at least half of the recognized needs will be adequately furnished by one capsule.

What I have tried to do in my advice to Wisconsin physicians is to point out that there are a number of vitamin pharmaceutical products which will provide half or more of the recognized materials. It is a little difficult if you try to make it exactly half because all of you have striven to get to that 4,000 or 5,000 units of A, 400 to 800 of D. I hope we can ultimately come to agreement so there will be a decrease in amount of variation between these products. It is improving if you compare these different multiple vitamin products as of April, 1943, with the situation that existed a couple of years ago. At least half of the recognized allowances of highest standards can be purchased at prices that vary between $4 and $6 per hundred daily doses. If one goes up into the next type, so that one capsule contains everything necessary of A, B, riboflavin, nicotinic acid and C and D, those are available now at costs that vary from about $6.25 to $8 per hundred. Now the spread between those two types is too small. That may not be too bad a commercial practice. I shall not debate that further.

I would like to suggest, however, that we ought to agree not only in our work, but in the practice of medicine, on the attempts to conserve these things because they are necessary and some of them are going to be critical and limited, and therefore we ought to be advising in terms of the minimum dose, which is really safe and not using tremendous excesses of material.

I believe there is a decreasing tendency of commercial firms to broadcast large amounts of new products for clinical trial, and I hope that that tendency can be made even more rigid or uniform. I am sure you recognize how impossible it is to get results that are really significant from broadcasting a few packages, let alone one package,

of a new product containing any one of these unidentified or unproved constituents of the B complex to be tried out. In the face of our present stringencies I think we ought to try to decrease that number so that these newer substances are really limited to people who have facilities for making careful studies and who can report those studies so they will be convincing to other members of the medical profession and also the pharmaceutical industry.

Natural and Synthetic Hormones

Among the hormones I shall go categorically through the whole group. First of all, I think synthetic thyroxin need not concern any of us since so little is used in the clinic and more than enough is available on the market. What about the production of U. S. P. thyroid? I do believe that there is still room for some careful work on other methods of standardizing thyroid than by the U. S. P. bio-assay of the iodine. That is a matter of interest for the future, not a pressing and urgent problem. There are at least three commercial laboratories that are interested at present in trying out parallel types of bio-assay, as well as chemical assay, in order to find out if there is something else to thyroid beside iodine determination.

The adrenal materials are in a very much more difficult position. Here we are dealing with extracts of glands of which there is a limited supply in comparison to the demand made on it, and which contain unusually labile materials, chemically speaking. The need for adrenal extract is far from being adequately supplied, and possibly greater than we realize, certainly greater than recognized in the case of Addison's disease at present. Chemical investigation of these extracts has shown the presence of steroids, resembling the sex steroids, with several different components identified. One of these that occurs in the very smallest amount in the adrenal happens to be the only one commercially available in synthetic form, desoxycorticosterone (DOCA).

This DOCA has been produced synthetically and widely used, but it has a couple of disadvantages. In the first place it does not do all that adrenal extracts do. That was debated a few years ago. Even its most ardent proponent of a few years ago will admit that it is inadequate as a complete adrenal substitute in human therapy. Its second disadvantage is that by overdosage phenomena it may cause actual harm, and this risk rises to the proportion of having a mortal-

ity. We don't like to face mortality from drugs, but we do have to face that situation unless DOCA therapy is very wisely planned. It may be lifesaving; it may also be death-dealing. It must be used with a great deal of caution. That is one reason to doubt its permanent advantage in medicine. A greater reason for this doubt is that DOCA does not give all of the effects that can be secured from the adrenal, of which there are at least three. There are at least three available commercial adrenal gland extracts on the market in this country at present.

But the problem gets even more difficult than that. There is debate as to how the activity of adrenal extracts shall be measured. Can it be measured in the terms of weight of glands from which the extract is made? I think that far from being satisfactory with the labile chemical substances from these glands. We want to know the activity there, not the source of the material. We must go back to the physiology of what adrenal cortex does. It does several things. It is life saving. It helps the body to hold sodium, and therefore to hold water, and therefore to maintain the fluid balance of the body. This property of controlling fluid balance, and of controlling sodium has been proposed as another method for bio-assay. It also enables the body to maintain a certain type of normal metabolism, and to convert protein into carbohydrates, which is an emergency function of the body. That has also been proposed as a basis of biological assay. The adrenal cortex is known to protect the body against the risks of certain kinds of injuries—almost any kind of prolonged or pronounced injury, cold, surgical shock, etc. It has some other more indirect effects. Even that protective device has been proposed also as a bio-assay technic.

In 1940 I was instrumental in bringing together the representatives of the different challenging points of view, five of them, to see whether we could get together on any one of them. If you have had experience in this adrenal cortex field you know some rather bitter arguments were going on between those different champions a few years ago. In this very building those five men sat down and had a dinner and talked this thing over for an evening. At the end of the evening it was decided that the way to resolve the problem was not to come to an agreement across the table; there was still a difference: five men and five means of measuring the same thing. Since that time there now appears a very different statement which is approach-

ing a consensus from those experienced in the field, that there are two types of adrenal cortex activity. There is a tendency to bring together life maintenance, sodium and water retention as one activity, and to bring together the transformation of protein to carbohydrates and muscular endurance as another. The resistance-to-shock effect may belong in this latter group with the carbohydrate factor. DOCA provides only the salt and water or life maintenance type activity. It is not the carbohydrate metabolism type. The extract of the glands shows both types of physiological action.

The problem is unsettled, and still will be until we can find agreement on assay methods. Can we get one assay method, or must we assay by two methods every adrenal cortex preparation, whether synthetic or from the gland, until we can get agreement? I think we shall need two. What is the answer? I think the answer is this: To try out the competing methods on each of the competing products, natural and synthetic, to find out if the response if there. Does one type of extract contain chiefly one component and another the other component? Can we measure the two things? We propose to do that. A conservative estimate called for $6000 for one year's work in three laboratories to test those out. Your firms producing the material agreed to provide the extracts. There was nobody to put up the $6000. There is where we are. I expect to return to the plan again.

In the case of the testicular hormones, we have a somewhat analogous situation. Testicular hormones are represented by essentially synthetic compounds, but standards of reference are needed for bioassays. As a matter of getting decisive proof on the source of testicular hormones, one steroid product in testicular extracts is identified fairly easily from interstitial cells. There is still a very definite debate in the minds of many, substantiated by data, which is not yet clean-cut and decisive, that there is another product of the testicle. What it is chemically or physiologically, or how important it is clinically, has not been determined.

Now all attention to testicle materials has been in terms of androgen assays. We know nobody can define this other possible testicular activity. In castrates testicle transplants will do certain things. Androgens will do most of those things, but not all of them. How can we compare them? We compare them by using certain effects on the prostate, the seminal vesicles or the cock's comb. There isn't a great deal of debate about those, but a fair consensus.

There is another assay which is of technical importance, that of the ketosteroids. Two sources of material in the body appear as one type of compound in the urine. We need a substance then to be used as the standard of reference for the assay of 17KS in the urine, which is becoming clinically significant in differentiating between certain kinds of cases. Another committee has been at work these last two years attempting to find out what can be used as a standard for bio-assay of steroid material. By a fortunate circumstance, during a discussion of the 17-ketosteroids last June, Prof. E. F. Cook happened to come in to the meeting for part of the time. The men who were available there were willing to undertake it, and it looks now as though we could provide, as sort of a joint proposal, an androgen standard. Manufacturers that have androsterone available, as a by-product or otherwise, will be asked to furnish material which would then be subjected to chemical identification for purity, and put into ampuls in standardized forms and deposited with the Revision Committee of the Pharmacopœia. It can then be issued to investigators, clinical researchers or manufacturers, or to the Government for the check-up of materials on the market. There would be a central repository of an accepted, permanent standard that has been identified and would become a reference standard. That seems to be one of the optimum ways of handling this problem of a debatable standard. Furthermore, it can be done on a self-liquidating basis, financed partly by the commercial organizations and partly by the sale of samples at a nominal fee to any laboratory that wants something for comparison with its product or for bio-assay. The fee for the material will repay the Pharmacopœia for the work. That is not official; it is a process being worked out, and I cite it as an example of what I believe will be a successful way to approach this matter of making available information from different points of view.

Another reason for having such a standard for androgen activity is that if and when somebody can discover another type of testicle extract which has biological activity, he can prove it really different. That will be true in any one of these hormone fields.

With the ovarian products we get into a greater multiplicity, and into very active commercial rivalries. We also get into debates about the activities of the material. Here we have accepted standards, but only three for a great number of types of ovarian products. We have standards for estrone and for estradiol benzoate, and the standard for

progesterone, all prescribed by the League of Nations Health Organizations. We know estrone and estriol are excretion products. Estradiol is far more potent and probably the original estrogen made by the ovary. We have very good commercial and clinical use for an impure mixture of estrogens, which is largely estrone, containing a small amount of estriol, and an uncounted number of other materials that are estrogenically active, making up less than 10 per cent of the total. That kind of mixture is now officially known (at the request of the Council) as Estrogenic Substance, and it is represented by a dozen or more commercial products under the head of Estrogenic Substances.

Now there is no accepted standard for estriol, except crystalline purity. No accepted biological standard has been available for estradiol; of course it can be made synthetically and crystalline pure. The same can be said of estrone, which can be made synthetically. It does have an international standard. There is no accepted standard for estrogenic substances. Why not compare the estrogenic substances containing the mixed estrogens with estrone? The reason is that each of these things has its own qualitative characteristic of action. One can use one rat unit of estrone and get one rat unit of any of these other compounds by comparison, if he does it as a definite technic. But vary the technic and one gets a different kind of an answer.

That is not satisfactory. It leads to commercial rivalry and all kinds of clinical uncertainties as well. The way around it would be to specify very exactly the conditions of assay. At present there is no formal agreement in this field. It is not satisfactory. The only proper way to solve this question is to specify established reference standards of estrogen and of estrogenic assay methods.

Now the clouds will get even thicker because of the introduction within the last year of another form of estrogenic substance, which is not hydrolyzed to give the steroid, but is a crude sulfate. It is orally active, and its characteristics of action are different from ordinary estrogenic substance. We have not heard from the last of the variations in natural estrogens.

Then come the synthetics, and the changes are being rung on them pretty rapidly in an attempt to get away from the nausea which is evidence of toxicity. I am sure we will see more synthetics. How are we going to compare them? Again we need to have some biological method by which we can characterize the type as well as the quantity of action of these compounds.

We tried to get agreement in the same fashion I described when speaking about adrenal materials, and the points of divergence were about as numerous. Some championed the rat, others the mouse as the assay animal. Again it calls for a few thousand dollars to pay for the work to decide the debate. The war came and stopped the work, even in private laboratories, which would aid this process. There is now a manuscript, which I had the privilege of seeing, coming from Dr. Curtis, with the Food and Drug Administration, on the statistical studies of the use of the rat or the mouse in the assay of pure estrone. Dealing with a crystalline substance, and using the rat, with the accepted technic, the error can be reduced to plus or minus 15 per cent, which I should say is very satisfactory for bioassay. Using the mouse instead of the rat, one can't approach that plus or minus 15 per cent. It would appear from the Curtis paper that the rat is distinctly superior. Now if the champions of the mouse agree, all right! There are some people who want to use mice because they are cheaper; others don't like mice because they stink, and so on.

Those are among the problems that are still unsolved and need to be tackled by some kind of a group which has authority and ability to go at these things. Food and Drug Administration staff members have suggested to me, in correspondence about this matter very recently, "Why should we worry about it? Why could we not go to clinical assay?" and "Why not compare these substances in women instead of rats or mice?" I don't know how many of you men have had clinical experience, or physiological tests on a great many women. To get a result whose error is plus or minus 15 per cent in women would baffle me. I am sure that women are more variable than that, in addition to which one would have to have women in numbers at least as large as the number of rats available. We could not depend on results in cases of spontaneous menopause, and we are castrating less women every year. I think it is a clinical impossibility to solve the assay problem using women.

I will say little about progesterone other than to indicate that it is being fairly satisfactorily handled by the League of Nations standard. Why should we not expect the League of Nations to manage all of these problems? The question answers itself. So far as doing anything like this is concerned, we, in this country, must attack our own problems at present. Maybe we will have to attack part of the problems for the rest of the world.

Insulin need not concern us greatly. Progress in insulin production, which will go on, is based on standard practice. Trials of standard, crystalline, protamine and globin insulins may well proceed. Though globin insulin and these others are being tried, from the point of bio-assay the situation is much more satisfactory because a very uniform, prescribed type of assay has been used from the first. Now this does not stifle progress because there has always been the possibility of using this one type of assay as a standard and setting up in parallel another type of assay. Having a standard assay promoted stability in the matter of production and comparison of different types of insulin, because it was prescribed by the originating group in the discovery of insulin.

The parathyroid interests me, but it may not interest most of you because the volume of use of parathyroid is so small. As I look at the industrial application of parathyroid, I am inclined to think the reason we know so little about it physiologically and from the standpoint of pharmaceutical manufacturers, is because there is so little of it used. It has been discovered that we can get around the difficulty attending the use of impure parathyroid by using big doses of vitamin D or other forms of irradiated ergosterol. I refer to the use of vitamin D in doses that vary from 50,000 to 400,000 units per day, orally, which sounds tremendous to you, I am sure. But we have been doing that for better than two years in a group of test cases, and we find no evidence of harm in any case. Doses are usually of 100,000 and 200,000 units; in one patient, 400,000 units. Now does that mean that there is no danger in administering 200,000 units of vitamin D daily to children as a prophylactic or in the treatment of rickets? I do not know. The situation may be different. We are testing it in the adult. At least there is no gross risk of toxicity as we formerly thought.

I think the problem ought to be reinvestigated as to how to prepare parathyroid. I do not believe the medical profession or pharmaceutical industry will be satisfied permanently with trying to substitute for a gland extract a synthetic reproduction of a vitamin. That's the way we are going at this. It works clinically. Therefore, I hope sometime some one or more of your laboratories will see fit to undertake the study of this relatively infrequently used gland extract, parathyroid, cleaning it up chemically and biologically so it is something respectable.

Posterior pituitary represents much more in the volume of production, but it is not a very difficult problem because here again we have, very fortunately, a prescribed standard U. S. P. method of bioassay both in terms of oxytocic and pressor activities, with the increasing consensus that there are two types of activities represented in the pituitary material of the posterior lobe. There are problems there for study. Of immediate interest are the recent slow acting posterior lobe preparations which have been made by combining the pituitary material with other factors. It is an application of the principle of slowing down the action by slowing down the absorption. I regret that this material was first introduced into clinical trials as a suspension of the active material in oils, for intramuscular injection. I wonder whether it could not have been done just as well as an aqueous suspension of the same thing. It is insoluble and a very slow digestive process releases the pituitary hormone.

There has been a very large vogue for the oil injections. I have been objecting for quite a while on the basis that some of the oils used (sesame, vegetable, etc.) are foreign bodies and cause foreign body reaction. The tacit assumption was made a few years ago that when deposited in a tissue oil stayed there and was slowly dissolved by tissue lipolytic enzymes. Unfortunately the oils stayed there merely as foreign substances in many cases, sometimes as globules with foreign body reactions about them.

Now there are a great many women, and a few men, walking around with these deposits in their tissues, and some of them have pain when they sit down, while others don't. I think the problem really ought to be investigated systematically. I have tried to get someone interested, to get funds. I have no facilities myself for doing this. Here again, I believe, is the kind of a proposition which ought to be backed, in a large part, by you men and your firms. What evidence can you adduce that the repeated use of intramuscular injection of oils is always safe? What happens to the material? We have seen enough work on animals to know some have definite foreign body reactions about them. I think it ought to be studied in different circumstances, not only for posterior pituitary, but any kind of material.

The anterior pituitary is, of course, the great field for debate. I suggest immediately that I think that we ought to agree that all thyrotropic and adrenotropic material, and other materials poorly understood, should be absolutely withheld from general clinical use and

sale. They ought to be restricted to the field of laboratory studies, and have controlled clinical investigation until we know what they are all about.

What pituitary products should be available commercially? I think there is good reason to say that growth-promoting materials should be available, as a few are, with enough clinical experience to justify their use. We are far from knowing all of the conditions under which they can be used well, but they can be used rather widely at present. Now the growth materials are all still crude. How far have they been reduced to crystalline purity? I don't know where the decision rests. The debate has gone back and forth. At present I think we will have to assume that potent growth promoters are crude. Several are on the market. Which is the best? I would tell you if I could. I do not know the answer, and so I am still employing materials, not from one laboratory, but from several laboratories.

Dr. Milton Lee, for a long time at Harvard Laboratory of Physiology, told me in confidence—what he wouldn't be willing to put in writing, much less in print—that one particular manufactured product was better than any other. Now that is his own version of working with one species of animal. That is not the kind of information, obviously, which can be used for a general decision. Yet we are trying to stimulate one thing: the growth of a human. Why shouldn't we have a definite growth unit? Here we have the debate, "What are we trying to make grow? Muscles or bones?" And it comes down again to reaching an agreement among the investigators on bio-assay methods. It could be achieved if we could bring together a few people vitally interested and experienced in this field, I am sure, to get some kind of a growth unit by which these things could be measured. I am almost certain you people would be interested likewise in having that done, if it could be done, so you would have a standard developed to use in your own comparisons, and in making material.

It is evident to me also that the Food and Drug Administration would welcome such standards. The Council on Pharmacy and Chemistry would welcome such standards. We would be able to say, "This is what it is claimed to be" or "This is not what it is claimed to be; it must be increased in potency or stability." Those standards need to be achieved. I do not need to argue that point further.

In the question of the gonadotropic material, we are confronted by greater difficulty, because there are probably two, possibly more

than two, gonadotropic substances in the pituitary. Until they can be identified with certainty, it is almost impossible to get agreement on how to measure X and Y, until we identify X as separate from Y. Until that can be achieved, we cannot solve this problem. And, again, if we can sit around the table with these gentlemen representing these different points of view, a working agreement can be secured. It is not necessary to get ultimate and final agreement on these things. We should have agreement, as a working agreement, subsequently to be revised and improved, because science keeps on moving. As I understand it, the Pharmacopœia represents the more stable type of agreement on such matters. We need a standard *pro tem.*, as we approach that more permanent position, in order to eliminate much of the chaos, both manufacturing and clinical. That is the burden of my argument, to present some of the different aspects of methods by which we can get together, if we raise the issues of improving bio-assay methods.

We have League of Nations standards for gonadotropic hormones from pregnant women, or from pregnant mares, but they are not the same as pituitary material, therefore their bio-assays will not suffice to extend to the pituitary. Specifically, what can be suggested for a mechanism to handle this problem of bio-assay of the pituitary? The Food and Drug Administration, as I understand it, does not set up methods. What they will do is use a method upon which there is general agreement, and watch for evidences of accuracy, stability, and so on. It must, therefore, move with a certain amount of precision and a certain amount of restraint to the adoption of methods so it will not be changing rapidly, but achieve stability.

It seems to me this Association might very well participate. I have discussed this thing with some of you personally, and with a good many other individuals, but I should like to throw out before you for your frank reaction the most recent suggestion that has come from one of the officials of one of your member companies, modified slightly in the course of our conversation. There should be set up a committee broad enough in its representation to enjoy the confidence and interest of all parties that have a stake here. This thing could very well be started by the only National Association in the field, the Association for Study of Internal Secretions. That Association appointed a committee in 1940, which is a continuing committee, with just this goal in view, but the committee has not achieved much, so far. On this committee now being suggested, would be a representa-

tive of the Association for Internal Secretions, a representative appointed by the Food and Drug Administration, a representative from the Council on Pharmacy and Chemistry, from the Pharmacopœia, possibly from the National Formulary, and a representative from this body. That group would attempt to work out plans by which a consensus could be arrived at on adrenal cortex, gonadotropins, progesterone, etc., so when these problems come up, and when it becomes evident to such a committee that work must be done, it can be done.

I think also it will be found important that rival methods must be tested out by two or more laboratories. It would become necessary to find who will and who can do it, and to find the funds to support the research. It is suggested that in the operation of this central steering committee, a contribution of a very moderate amount for ordinary operating expenses might be expected from the Council on Pharmacy and Chemistry, and the Pharmacopœia, the National Formulary, and from this body, realizing that we cannot ask for a contribution like that from the Food and Drug Administration or the Association for the Study of Internal Secretions. They have no funds.

When it comes to the prosecution of actual investigation to settle such points at issue, we should have to look for further specific grants. Whether those funds should be asked for from the Foundations, or from members of the Industry, is open for debate. I think it is evident, however, to all of us that the cost of this type of activity is a perfectly proper part of the cost of producing hormones for use commercially. Therefore it is a manufacturers' cost. It also is a perfectly proper cost of the regulatory activities of the government, and also it is a perfectly proper cost of the material to the consumer, and it is a perfectly proper cost to the physician for the materials that he wants to use. You can argue any one of those you please, but the question is, "Where do we find the money we need to do the work?"

In this field of constantly increasing volume of production, there is also an increasing volume of problems that come up. I do not believe they can ever be worked out satisfactorily until we work together. If by some means we find methods of cooperation, I should be very happy to participate.

THE DEPROTEINIZATION OF BEEF PLASMA BY MOLECULARLY DEHYDRATED PHOSPHATES, AND SOME PROPERTIES OF THE PRECIPITATE FORMED *

By A. A. Horvath **

PHOSPHATES, whose molecules, when considered as acids, contain less water in proportion to phosphorus pentoxide than orthophosphoric acid, are designated as molecularly dehydrated phosphates. (1)

In 1816 J. J. Berzelius (2) discovered that phosphoric acid, known today as metaphosphoric acid, possesses the property of coagulating egg white. Experimental work by a number of European authors, and in our country by Folin and Denis, (3) showed that the so-called metaphosphoric acid (glacial phosphoric acid, $HPO_3 . NaPO_3$) was remarkably effective as a precipitant for blood proteins. Its use, however, has mainly been confined to deproteinization of blood for vitamin C determination, replacing trichloroacetic acid which causes oxidation of vitamin C and decolorization of the dichlorphenolindophenol reagent.

The objective of the present investigation was to secure information on deproteinization of blood by a number of complex phosphates available today, and to study the properties of the respective protein-phosphate compounds.

Experimental

(A) Two cc. portions of citrated beef blood plasma were diluted with 8 cc. water, and precipitated by 0.8 cc., 1.00 cc., 1.2 cc., and 1.4 cc. of a 10 per cent solution of acid phosphate glass, having a Mol ratio of $Na_2O/P_2O_5 = 0.715$ (pH of a 1% soln. = 2.2). When 0.8 cc. of phosphate solution was added, the pH was about 4.0, the precipitation of proteins was incomplete, and on centrifuging the supernatant fluid was milky. The addition of 1 cc. of phosphate glass

*Presented at the 1943 Spring Meeting of the American Chemical Society.
**Chief, Pharmacology Section, Hall Laboratories, Inc., Pittsburgh, Penna.

solution gave a pH of approximately 3.8, and the preciptation of proteins was nearly complete. 1.2 cc. of acid phosphate glass gave a pH of 3.6, and produced a complete precipitation of the proteins.

(B) Solutions of crystalline sodium-trimetaphosphate and of crystalline sodium-tripolyphosphate produced clear filtrates in diluted blood plasma at a pH of approximately 3.8, but after standing there appeared gradually in the filtrates thread-like bodies of protein nature, which developed into flocculent precipitates, an indication that the precipitation was incomplete. The thread-like bodies from the sodium-trimetaphosphate filtrates showed double refraction.

(C) Two cc. portions of citrated beef blood plasma, diluted to 10 cc., were treated with 0.1, 0.2, and 0.3 cc. of a 10 per cent solution of sodium phosphate glass of pH = 6.5 ("Medi-Calgon")* and acidified by HCl (4%) to a pH of 3.8, which, as well as lower pH values, was found to be suitable for the precipitation of serum proteins. Complete deproteinization was observed where 0.2 and 0.3 cc. portions of Medi-Calgon were used. A dilution of the plasma of 1:4 or higher was found to facilitate the completeness of deproteinization.

(D) The protein-Calgon precipitate was washed several times with distilled water with centrifuging, and its suspension in distilled water was found to dissolve almost completely in concentrated solutions of NaCl, Na_2SO_4, and $(NH_4)_2SO_4$, as well as in solutions of $CaCl_2$, $BaCl_2$, $MgSO_4$, $Al_2(SO_4)_3$, Alum, and $FeCl_3$. On heating to 80° C. or higher, there separates from such solutions a voluminous precipitate of protein nature.

Protein-Calgon, as well as protein-trimeta-, or tripolyphosphate, dissolve very readily in urea solutions, and these remain clear on boiling. The addition to such a urea-protein-Calgon solution of dilute acid, formaldehyde, or of a concentrated solution of NaCl, Na_2SO_4, or $(NH_4)_2SO_4$, causes the formation of a flocculent precipitate.

It was found that plasma protein-Calgon, when properly washed, is soluble in urea, when prepared at a pH range from 4.0 to 2.0. On the other hand, the solubility of the washed serum protein-Calgon in concentrated solutions of neutral salts of monovalent metals depended upon the pH at which it was originally prepared, being insoluble when

*Medi-Calgon is a phosphate glass having a Mol ratio of $Na_2O/P_2O_5 = 1.1$. For convenience, this glass is also called here "Calgon".

obtained at pH values of 3.0 or less. The ageing of the protein-Calgon, even when washed, affected adversely its solubility in neutral salts solutions.

The plasma protein-glassy phosphate compounds dissolve when brought to a pH of approximately 6.2 by solutions of NaOH, Na_2CO_3, or NH_4OH. Such solutions remain clear on boiling, but a precipitate is formed on acidification, as well as on the addition of a neutral salt solution, or of formaldehyde.

Protein-Calgon, dissolved at a pH of 6.2, forms on reacidification a voluminous gel-like precipitate, which tends to contract on standing.

Protein-Calgon, dissolved at a pH of 6.2, possesses the capacity of completely deproteinizing blood serum at a pH of 4.5, forming a compact precipitate.

Two samples of plasma-Calgon were washed, their suspensions dissolved in solutions of $(NH_4)_2SO_4$ and $MgSO_4$, and dialyzed in viscose tubing for three days, with the following results: The first sample had a pH of approximately 6.5, was not coagulated by heat or acid, could be precipitated by solutions of $(NH_4)_2SO_4$ and small quantities of $Al_2(SO_4)_3$, but redissolved in an excess of the latter, even on boiling. The second sample had a similar pH, and was coagulated by heat and by acid, but was not precipitated by $(NH_4)_2SO_4$. The behavior towards $Al_2(SO_4)_3$ was similar to that of the first sample.

All of the reported experiments were repeated with a 2 per cent solution of egg albumin, and similar results obtained. Some studies on hemoglobin were also conducted.

Discussion

According to Perlmann, (4) proteins combine with metaphosphoric acid to form an insoluble precipitate, in which the phosphorus content is equivalent to the number of the positively charged groups of the protein, a fact which has been previously made use of by Schofield (5) for the titration of ionizable amino groups in proteins. Briggs (6) concluded from his studies that the whole phenomena of metaphosphate-binding by proteins seems to be intimately associated with the polyvalent character of the protein and the metaphosphate, and found it having many characteristics of a complex coacervate, which would explain the dissolving action of added neutral salts. The same author found the titration curve of the protein-metaphosphate to be revers-

ible, and stated that no denaturation of the protein occurs through the action of metaphosphate. Perlmann and Hermann (7) were, in fact, able to recover from egg albumin-metaphosphate crystals of egg albumin, which had the same appearance as normal egg albumin, were free from phosphorus, and were found to contain the same amount of amino-nitrogen.

These data are suggestive of the potential value of glassy phosphate for the isolation of proteins, or of some protein fraction, from beef blood plasma, which would be suitable for blood transfusion purposes. The incomplete precipitation of serum proteins by trimeta- and tripolyphosphate in acid medium is probably due to some globulin fraction, and thus the constituents which render beef blood protein not entirely safe for transfusion purposes might perhaps be eliminated. According to Horvath and Little,(8) there are slightly less total globulins in cows' plasma than albumin.

The fiber-like bodies, which were observed to develop in the filtrates from plasma-trimetaphosphate precipitation, consist presumably of oriented molecules, since they show a crystalline structure in polarized light, and it seems likely that here the peptide molecules are linked by phosphate polymer chains. The peptide molecules might also have consisted of polypeptides or secondary albumoses, since these, as well as peptones and amino-acids, are not precipitated by metaphosphoric acid.

Due to this property, the so-called "nonprotein nitrogen" fraction in filtrates from plasma, deproteinized by metaphosphoric acid, is much higher than in filtrates from trichloroacetic acid, not to mention the filtrates from tungstic or phosphomolybdic acid. A convenient test, permitting the estimation of this "extra" nitrogen from metaphosphoric acid filtrates, could be developed by their subsequent treatment with phosphomolybdic acid, and by measuring the turbidity obtained. Such a test would be of importance for the diagnosis and treatment of pathological conditions where there exists an increase in the polypeptide fraction of the blood. In recent times suitable tablets from sodium phosphate glass plus an acidifier for deproteinization purposes have been developed.(9)

The property of protein-Calgon, dissolved at a pH of 6.2, to precipitate completely natural protein at a pH of 4.5, as against 3.8 for Calgon as such, suggests the possible enmeshing of the natural protein by the protein-Calgon structure. This phenomenon could find

an application in the treatment of wounds and burns, especially in view of the fact that protein-Calgon is resistant to putrefaction, and that the protective film may be removed by solutions of neutral salts or by urea.

Summary and Conclusions

1. Solutions of sodium-metaphosphate glass ("Medi-Calgon", having a pH of 6.5) cause complete deproteinization of dilute blood plasma (1:4 or more), at a pH range of 3.8 and less, and the filtrates remain clear on standing.

2. The washed precipitate dissolves in solutions of mono-, di-, and trivalent neutral salts, from which flocculent protein precipitates separate out at 80° C. and above. The protein-Calgon is also soluble in urea solutions.

3. The plasma protein-Calgon dissolves when brought to a pH of 6.2 by alkalies. Such a solution remains clear on boiling, but a precipitate is formed on acidification, as well as on the addition of neutral salt solution, or of formaldehyde.

4. Deproteinization of blood by Medi-Calgon is not only simple and convenient under field conditions, but it provides also additional nitrogen fractions in the filtrate.

REFERENCES

1. C. Schwartz and C. J. Munter. *Ind. Eng. Chem., 34*:32 (1942).
2. J. J. Berzelius. *Gilbert's Ann., 53*:393 (1816).
3. O. Folin and W. Denis. *J. Biol. Chem., 26*:491 (1916).
4. G. E. Perlmann. *J. Biol. Chem., 137*:707 (1941).
5. R. K. Schofield. *Trans. Farad. Soc., 31*:390 (1935).
6. D. R. Briggs. *J. Biol. Chem., 134*:261 (1940).
7. G. Perlmann and H. Hermann. *Bioch. J., 32*:928 (1938).
8. A. A. Horvath and R. B. Little. *J. Clin. Invest., 5*:541 (1928).
9. U. S. Patents 2,171,961 (1939); 2,171,962 (1939); 2,208,096 (1940).

SUGGESTING ISOPROPYL ALCOHOL IN TWO OFFICIAL LINIMENTS

By R. C. Clouse and M. W. Bamford

SHORTAGES of materials have prompted changes in the formulas of several official preparations. The possibility of further conservation of ethyl alcohol as well as the chance of finding a way to by-pass the increasingly stringent regulations in the use of specially denatured alcohol induced us to experiment on the use of isopropyl alcohol in the manufacture of Liniment of Soft Soap and Liniment of Camphor and Soap.

Isopropyl alcohol has been used for several years in rubbing compounds as a substitute for ethyl alcohol. New and Nonofficial Remedies (1943) states that "Recent investigations indicate that isopropyl alcohol compares favorably with ethyl alcohol so far as antiinfective action is concerned." These evidences of the safety of its use and its effectiveness in skin sterilization together with its solvent properties seem to justify its use for the purposes we propose.

We are submitting formulas for the products which seem to us to be the most satisfactory of our experiments. In the case of Liniment of Soft Soap we found that there is much objection to the odor of oil of cedar which is used in the new official formula. We therefore substituted oil of bay and since this did not disguise the odor of the isopropyl alcohol to our satisfaction we also added two per cent of ether. In addition to improving the odor this enhances the solvent, detergent and disinfectant properties of the preparation.

The formulas we propose are as follows:

LINIMENT OF SOFT SOAP

Medicinal Soft Soap	650 gm.
Oil of Bay	10 cc.
Ethyl Oxide	20 cc.
Isopropyl Alcohol sufficient to make	1000 cc.

Liniment of Camphor and Soap

Hard Soap, dried and granulated or powdered	60 gm.
Camphor, in small pieces	45 gm.
Oil of Rosemary	10 cc.
Isopropyl Alcohol	700 cc.
Distilled Water sufficient to make	1000 cc.

For both formulas the procedure is the same as for the official preparations.

The Liniment of Camphor and Soap makes a satisfactory Chloroform Liniment.

The cost of these preparations is less than that of the same products made with specially denatured alcohol, and the elimination of the specially denatured alcohol will make it possible for the retail pharmacist to make these liniments in small quantities.

Further experimentation might develop products in which the odor of the isopropyl alcohol is more completely masked, but we consider them quite satisfactory and are submitting them to the Revision Committee of the Pharmacopœia for consideration.

SELECTED ABSTRACTS

A Principle From Liver Effective Against Shock Due to Burns. M. Prinzmetal, O. Hechter, C. Margoles and G. Feigen. *J. A. M. A. 122,* 720 (1943). Preliminary experiments on rats and mice subjected to a standardized technic of producing shock by scalding indicated that the intraperitoneal administration of a commercial liver extract containing 15 injectable U. S. P. antianemia units definitely decreases the mortality which follows burns and significantly increases the average survival time. The liver preparation was given in a dose of 1 cc. per 100 gm. of body weight one-half hour before the animals were scalded.

That the antishock activity of liver extract is not due to the antianemia principle was shown by the administration of a highly purified liver extract in amounts equivalent to the antianemia activity of 15-unit liver extract.

The antishock principle has not as yet been isolated, but evidence has been accumulated that it is (1) relatively thermostable, the activity remaining undiminished after boiling aqueous solutions for 20 minutes, (2) not destroyed by aeration at high temperatures, and (3) soluble in water but precipitated from aqueous solution by acetone or ethanol.

The principle does not consist of choline, which is present in liver extracts, since tests on this substance show it to be inactive against shock.

The intraperitoneal administration of 15-unit liver extract after the onset of shock was found to be therapeutically effective only occasionally. This is probably due to the fact that commercial liver extracts contain large amounts of extraneous tissue constituents which are likely to be deleterious to animals in shock.

The mechanism by which 15-unit liver extract exerts its antishock activity is unknown.

A Statistical Study of Minor Industrial Burns. R. D. McClure and C. R. Lam. *J. A. M. A. 122,* 909 (1943). The study of 5,609 cases of minor burns suffered by employees of three large companies engaged in war work revealed that 84 different substances, many of which were proprietary remedies, were used in the treatment of these injuries. Despite the fact that a dressing possessing a lubri-

cating quality would seem to be better adapted to the purpose of keeping workmen on the job, tannic acid jelly was widely used. One brand was used in 560 cases, each patient receiving an average of 5.6 treatments; the average healing time was 7 days. Another brand of almost identical composition was used in 347 cases, with an average healing time of 3.7 days.

Boric acid ointment was employed in 182 cases, each of which received an average of 2.3 treatments; the average healing time was 2.5 days. Plain petrolatum was used in 32 cases; the average number of treatments was 1.7, and the healing time 2 days. Zinc oxide ointment was the preparation of choice in 73 cases, the average number of treatments being 4.6 and the average healing time 6.4 days. A proprietary preparation containing 11 drugs in a petrolatum base was used in the treatment of 1,285 burns, but was not found superior to any of the emollient remedies. The average number of treatments was 3.8 and the average healing time 6.3 days.

"Foille," a proprietary product consisting of a number of drugs in a water-in-oil emulsion, was employed in 403 cases, with an average of 5.3 treatments per case and an average healing time of 5.9 days.

While the medical literature contains a number of reports of the clinical use of ointments containing cod liver oil in burn cases, this class of preparation was not widely employed in this study. A commercial product of this type was used in 25 cases, with an average healing time of 3.1 days. Another commercial ointment containing vitamins A and D was used in 41 cases, with an average healing time of 3.2 days.

There was no evidence in this study that the local use of sulfonamides is of value in the prevention of infection in burn cases. Ointments containing drugs of this class were used in 299 cases, with an average healing time of 4.1 days.

The authors recommend the following treatment for minor industrial burns: (1) wash the area with white soap and water; (2) do not break blisters or otherwise debride the wound; (3) cover with fine mesh gauze impregnated with petrolatum or 5 per cent boric acid ointment; (4) apply a firm dressing over this, bulky enough to keep dirt away from the injury but not so large as to keep the workman idle.

Intensive Human Serum Treatment of Burn Shock and a Modified Formula for Calculating the Amount of Infusion. D. L. Presman, M. Janota, R. E. Weston, S. O. Levinson and H. Necheles. *J. A. M. A. 122,* 924 (1943). The authors believe that recent clinical experience has demonstrated that the usual plasma or serum therapy of burn shock is inadequate and that all the formulas for computation of fluid replacement understate the amounts required in extensive burns.

The treatment of two patients who had suffered second degree burns covering, respectively, 45 and 50 per cent of the body area is reported. During the first 20 hours neither patient took fluids by mouth. Each received 1,750 cc. of normal serum during the first four hours after the burn; during the following 64 hours each received an additional 2,500 cc. of serum plus 6,000 cc. of a solution containing 0.9 per cent. sodium chloride and 5 per cent. dextrose. Calculation of the plasma volume of each patient revealed that during the 68 hours following the injuries serum infusion equivalent to 140 per cent of the calculated plasma volume in one case and 181 per cent in the other had been administered.

The movements of blood proteins following the burn were as great as those of the body water. Immediately following the serum administration (containing 7.5 per cent. protein) four hours after the burn, the plasma protein of each patient was normal or slightly above. However, during the course of treatment, one patient received 93 gm. and the other 143 gm. more than the calculated normal total plasma proteins. In addition, after the third day both patients were placed on a diet high in protein and vitamins.

Simultaneous analyses of blister fluid and of blood plasma were performed during the treatment of three patients in whom, respectively, approximately 5, 10, and 45 per cent of the body surface had been burned. It was found that blister fluid contains a concentration of proteins equivalent to 70 to 80 per cent of the plasma proteins. Although the albumin content of blister fluid was fairly constant, the globulin content showed variations which were independent not only of the albumin content of the blister fluid but also of the globulin and albumin values of the blood.

The authors suggest that in the treatment of extensive burns in adults 50 cc. of serum (or 60 cc. of plasma) for every per cent of body surface burned should be administered immediately. In addi-

tion, during the first 24 hours 20 to 30 cc. for every per cent should be given, and another 20 to 30 cc. in the first 72 hours. Crystalloid fluids should not be given during the first 24 hours. Fluids and a high protein diet by mouth should begin as soon as possible.

Wound Healing and Infection After Local Implantation of Sulfonamide Powder. J. A. Key. *J. A. M. A. 122,* 1003 (1943). To support the contention that it should be routine practice in all civilian and military hospitals to implant a sterile sulfonamide powder in clean operative wounds, the author reports a series of over 600 cases in which this technic was successfully followed. The drug of choice was sulfanilamide in the first 150 cases, sulfathiazole in the next 100 cases, and finally mixtures of the two drugs in various proportions.

Postoperative complications occurring in the entire series included three deaths, two infections, one separation of wound edges, five hematomas requiring evacuation, two hematomas evacuated and resutured, and two stitch abscesses. There were no toxic symptoms except fever, which was present in about 5 per cent of the cases, and which may or may not have been caused by the drug. Postmortem examinations revealed that the deaths which occurred were in no way related to the use of the drug or to infection. A brief discussion of the cases presenting the complications mentioned above is given.

In the other cases the wounds healed in a normal manner without excessive scar formation. Use of the drug is believed to have shortened the average period of hospitalization. It is possible that the use of an excessive amount of the sulfonamide may delay the healing of the wound. Not over 10 gm. were used in any of the wounds treated.

The author prefers sulfathiazole for use in wounds contaminated with staphylococci, but finds sulfanilamide equally satisfactory for clean wounds. On theoretical grounds a mixture of two parts of sulfanilamide and one part of sulfathiazole is chosen for the treatment of clean wounds.

The Treatment of Early Syphilis by the Concurrent Administration of Arsenic and Bismuth in a Period of Five Days. H. Rattner. *J. A. M. A. 122,* 986 (1943). The author reports the re-

sults of the five-day treatment of early syphilis seen in 481 cases, of which 421 completed the full course of medication. During the earlier part of the study mapharsen alone was used, being administered intravenously by the drip method over an eight-hour period in a daily dose of 0.24 gm. dissolved in 2,000 cc. of 5 per cent dextrose solution regardless of the age, weight or sex of the patient. Since a single course of the treatment failed in from 12 to 15 per cent of the cases, the technic was modified so as to include daily intramuscular injections of bismuth sodium tartrate in an amount equivalent to 22 mg. of bismuth. The combined treatment reduced the incidence of failures from one course of medication to 6.5 per cent.

Although there were no fatalities in the group, there were serious reactions in four cases treated with mapharsen only: two patients developed encephalopathy with transitory hemiparesis after completion of the treatment; the third experienced a single convulsion after three days of treatment; the fourth, on the completion of only one day's treatment, exhibited acute glomerulo-nephritis, anuria, uremia, hepatitis and pericarditis.

Twenty-three patients were given a second course of treatment because of relapse, reinfection, or serofastness. No allergic reaction nor other complication was noted.

The study emphasized the value of reliably performed quantitative serologic tests as a therapeutic index.

Sulfonamiduria; a Simple Test for Its Detection. E. Bogen. *U. S. Naval Med. Bull. 41,* 1135 (1943). A convenient test for the presence of a sulfonamide in the urine is necessary for routine or field use in military or naval operations. The author recommends the lignin test as suitable and reliable. A drop of urine is placed upon a piece of wood-pulp paper and a drop of hydrochloric acid is added. The appearance of a yellow color is positive for the presence of a sulfonamide; this is read as 1-plus, corresponding to about 0.01 per cent of the drug. A deep yellow color (2-plus) corresponds to about 0.05 per cent; an orange yellow (3-plus), to 0.1 per cent; and an orange color (4-plus) to 0.5 per cent or more.

Nothing which is likely to occur in the urine has been found to give a false positive test. No positive tests were obtained with inor-

ganic substances, alcohols, aldehydes, acids, alkaloids, hormones, or vitamins. The marked color of the dyestuffs was found to preclude the possibility of reading the test.

A positive reaction was obtained with sulfanilamide, sulfapyridine, sulfapyridine sodium, sulfathiazole, sulfathiazole sodium, sulfadiazine, and sulfaguanidine; but with prontosil and neoprontosil the test was obscured by the color of the dye itself. A positive test was also observed with each of the following substances: aniline, benzidine, hydrazine, naphthylamine, *o*-tolidine, *p*-dimethylaminobenzaldehyde, *p*-aminobenzoic acid, sulfanilic acid, procaine, benzocaine, and larocaine. None of these, however, has been encountered in urine in a concentration sufficient to yield a positive test.

As an additional check the sediment obtained by centrifuging a specimen of urine may be examined microscopically for the presence of crystals characteristic of a particular sulfonamide.

Studies on the Improvement of Wound Therapy by the Use of Synergistic Mixtures of Antibacterial Substances. L. A. McClintock and R. H. Goodale. *U. S. Naval Med. Bull. 41,* 1057 (1943). Experiments *in vitro* showed that urea in a concentration of 6 gm. per cent prevents the inactivation of sulfanilamide (125 mg. per cent) by *p*-aminobenzoic acid in concentrations ranging from 0.5 to 15 mg. per cent, determined on *Staphylococcus aureus.*

It further appeared from studies made both *in vitro* and *in vivo* that urea and also two substituted phenols (2-chloro-4-phenyl-phenol and 3, 4, 5, 6-tetrabromo-*o*-cresol) act synergistically with sulfanilamide to inhibit bacterial growth in concentrations considerably below the minimum effective bacteriostatic level of each of the compounds alone.

Diffusion studies performed *in vitro* upon both living and dead strips of abdominal muscle tissue of the rabbit revealed that urea increases the rate of dialysis of sulfanilamide in saline solution.

It was found that aqueous solutions of urea exert a solubilizing effect upon the sulfonamides. For a concentration of 50 gm. of the former per 100 cc. at 30° C., the following percentages of concentration were observed: sulfanilamide 8 per cent; acetyl-sulfanilamide 4.4 per cent; sulfathiazole 1.8 per cent; sulfapyridine 1 per cent; sulfaguandine 2.6 per cent; sulfadiazine 0.3 per cent.

Control of Blood Coagulability With Coumarin and Other Drugs. J. E. Rhoads, J. Walker and L. Panzer. *Northwest Med. 42,* 182 (1943). Dicoumarol or 3,3'-methylenebis-(4-hydroxycoumarin) possesses advantages over heparin as an anticoagulant in that it may be administered orally and its action is more prolonged. In the dog the maximum depression in the prothrombin concentration occurs about 48 hours after the drug is given, and the effect persists in diminishing degree for approximately one week. In contrast, the effect of heparin in the dog lasts but 80 minutes.

The effective dose of dicourmarol in man is probably between 300 and 600 mg. Since the drug is capable of producing hemorrhagic phenomena if used for a long period of time, frequent prothrombin determinations are necessary. On the first day of treatment 300 mg. of dicoumarol are given, followed by 200 mg. more in 24 hours. On the third day no drug is given until the prothrombin time has been determined; if it is over 90 sec. the drug is withheld. A prothrombin time of 60 to 90 sec. indicates the administration of an additional 100 mg., while if it is below 60 sec. 200 mg. are given.

Vitamin K is not an antidote for dicoumarol in the sense that protamine is an antidote for heparin. The hypoprothrombinemia produced by dicoumarol is resistant to the vitamin, making necessary the use of blood transfusions to elevate the prothrombin level.

It was found advantageous to combine the use of dicoumarol with heparin, since a sustained heparin effect in the coumarinized patient may be maintained for as much as 24 hours without the use of continuous intravenous infusion for the latter drug. In addition, the use of dicoumarol permitted the intramuscular administration of heparin in smaller doses than is otherwise possible.

SOLID EXTRACTS

Essential and Interesting Information From Many Sources

Pharmaceutical manufacturers are expanding their productive capacity for penicillin tremendously. At present the quantities available are almost insignificant in view of the tremendous demand for this extremely potent antibacterial substance and practically none is available for civilian consumption. Since today it can be produced only by the cultivation of Penicillium notatum and its yield is very small, production on a really extensive basis must await the elaboration of its chemical structure and the development of a method of synthesis. This may take years or it may completely baffle the chemist as has insulin for many years.

AJP

Cellophane is now being used to fashion protective clothing for workers. It is not affected by petroleum solvents or acids and it also provides good protection against war gases. The disadvantages that it possesses of being inflammable and affected by water are overcome by flameproofing it with ammonium sulfamate and waterproofing it with a resin.

AJP

Many undiagnosed illnesses of yesterday would be classified today as allergies. As a matter of fact, in the light of the newer knowledge of the subject, it is estimated that 10 per cent of the population is allergic to one or more substances, and that from 30 to 50 per cent of human beings manifest evidence of minor idiosyncracies.

AJP

It is commonly accepted that scientific research is responsible for all of today's comforts, and, too, for many of its discomforts that are war-born. This latter phase, however, is not the fault of science and cannot be charged to it as a demerit. All in all, we can be thankful that there have been men and women in this world who have

worked hard in the various fields of research, agreeing with the great pharmacist-chemist Scheele, who voiced the sentiment away back in the 18th century: "Some hold that there remains no further hope of searching out the elements of substances. Poor comfort for those who feel their greatest pleasure in the investigation of natural things. For mistaken is anyone who endeavors to confine chemistry, this noble science, within such narrow bounds."

AJP

There are about thirty-five species of Madder plants, members of the family Rubiaceæ, found abundantly in Asia and Europe. It was the red dye from this plant with which the trousers and capes of the entire French army were colored in 1840 by order of King Louis Philippe. Prior to that the English soldiers had dyed their coats in like manner, giving rise to their nickname "Redcoats".

AJP

A recent issue of the Pharmaceutical Journal *tells us that the supply of aspirin to manufacturers and wholesalers in England is on a strict allotment basis, and the notice warns pharmacists against the temptation to enter into Black Market arrangements with small manufacturers who have no allocation. In the same issue of the* Journal *we read also that one Englishman committed suicide this year by consuming 500 aspirin tablets, a woman ended her life by taking 300 aspirin tablets, and another death, undetermined as suicide, occurred when a man took an excessive dose of this same drug. It looks like a case of feast and famine on the same island.*

AJP

Paper packets of sulfanilamide are now given to America's fighting men for possible emergency use on the battlefield. The envelopes in which the 5 gm. portions are enclosed are sealed with a substance based on Vinylite resin. Once sealed, it is practically impossible for the envelopes to come open through failure of the sealing substance. Even sterilization with live steam will not loosen the heat-sealed bond.

July 2, 1943, marks the one hundredth anniversary of the death of Samuel Hahnemann, founder of homeopathy. Early in his life this man, whose teachings and theories are still endorsed by many, wrote a dictionary for apothecaries. He studied medicine at Leipzig and Vienna and practiced his profession in Dresden and later in Leipzig. After eight years of practice, however, he became imbued with the thought that ordinary methods of treatment of that day were elusive in nature, and, accordingly he felt compelled to relinquish his practice. From that point on, using some of his own thoughts and amplifying the thoughts of a number of men who had preceded him, he built up his own new system of medicine.

AJP

It has been announced that a further development of the naphtha isomerization process has resulted in a new and better method for the manufacture of neohexane. Neohexane is a hydrocarbon of superior anti-knock properties which, when incorporated with aviation blends of gasolines, makes a splendid, much-needed super-fuel for airplane use. Further development of the use of the airplane in wartime and in peace may be possible from this new manufacturing process.

AJP

Many shipyard workers, most important people in our current war effort, have been afflicted with epidemic keratoconjunctivitis, an inflammatory disease of the eye. Until recently, a virus had been suspected as being the causative agent, but no particular one had been identified as the offending body. Recent investigations along the West Coast, however, where the disease has been quite prevalent, showed that the infectious agent could be maintained by first inoculating mice with scrapings and then transferring the mouse brain emulsion from the second mouse passage into tissue culture. It is hoped that the investigation of these two strains will throw additional light on the specificity of the offending agent.

BOOK REVIEWS

A Text-book of Inorganic Pharmaceutical Chemistry. By Charles H. Rogers, D. Sc., Dean of the College of Pharmacy, and Professor of Pharmaceutical Chemistry, University of Minnesota. Third edition, thoroughly revised, 1943. Octavo, 704 pages, illustrated with 52 engravings. Cloth, $7.50, net. Lea & Febiger, Philadelphia, Pa.

The many changes in the U. S. P. XII and the N. F. VII necessitated a complete revision of this standard text, and in this task the author has succeeded admirably. Apart from bringing the present edition up to date by including the latest physical constants of the substances considered, presenting the necessary text material on the new official substances or preparations, and discussing recent advances made in industrial manufacturing methods, the author has made certain changes which should improve the book from the standpoint of both the teacher and the student. Ionic equations have been used under the Tests for Identity of the ions of metals and non-metals, instead of the molecular equations presented in the second edition. However, the latter type of equation has been retained both for the Tests for Identity of the individual compounds and for the discussion of Industrial Methods of Manufacture. An added feature of the third edition is the inclusion of all the inorganic salts of the organic acids recognized by the U. S. P. XII and the N. F. VII.

The general plan of the present edition is identical with that of the second, *viz.*, the presentation of introductory or historical material on a given element, its occurrence, physical and chemical properties, commercial production, tests for identity or for purity, explanation of its assay, and its pharmaceutical preparations and uses. As before, the elements are considered according to their groups in the periodic table; their compounds are taken up in logical order under each heading. Where necessary, cross references are provided.

In the discussion of Carbo Activatus, page 478, appears the statement that the adsorptive power of this substance for gases dissolved in water is tested upon an aqueous solution of sulfur dioxide. It is

to be noted that this test, official in the U. S. P. XI, was deleted from the Second Supplement to this revision, and has not been included in the U. S. P. XII.

A minor point may be mentioned in connection with the Table of Contents, pages 23 and 24. Cobaltous nitrate, sulfate, and sulfide are listed under the heading "Halogen Salts" (of cobalt); the same type of listing is given to certain iron compounds. Nickelous chloride and sulfate and nickel sulfide are similarly listed under "Oxides and Hydroxide" (of nickel).

Within its scope, the present edition should prove a valuable study aid to the student of pharmacy, and as a refresher for the pharmaceutical or medical practitioner of several years standing.

A. A. DODGE.

The Microscope and Its Use. By Frank J. Muñoz and Dr. Harry A. Charriper. 1943. 334 pages, including index. Illustrated. Chemical Publishing Co., Inc., Brooklyn, N. Y.

Described as a technical book on the microscope in non-technical language, its purpose being to instruct in the use and care of simple and specialized microscopes, microtomes and their attachments.

The various chapters deal with the history and development of the microscope, the modern microscope with its use and care, types of illumination, the use of specialized instruments such as the stereoscopic, metallurgical and polarizing microscopes, and the care and use of microtomes. The illustrations in the book are largely taken from the catalogues and literature of microscope manufacturers. A few are original.

Of especial interest are the chapter on common errors in the use of the microscope, the check list of difficulties encountered during section cutting and the extensive glossary of terms used in relationship to the microscope.

The book is not to be considered as a text on microtechnique, but rather as a book describing the various instruments and their accessories, their care, use and special applications in the biological sciences and industry.

Manual of Clinical Therapeutics: a Guide for Students and Practitioners. By Windsor C. Cutting, M. D., Associate Professor of Therapeutics, Stanford University School of Medicine, San Francisco, California. 1943. W. B. Saunders Company, Philadelphia, Pa.

Today more than ever in the past medical men have less time to present themselves for post-graduate study. If one were to name the subject most vital to practitioners he would consider therapeutics the leader. Therapeutics has received much attention, and the progress made in the past ten years has been tremendous. Encompassing this change, Dr. Cutting brings the discussion of therapeutics up to date.

The author, in an uncanny fashion, carries the student,—undergraduate, graduate, or post graduate,—along through every phase of therapy. In addition to complete and concise descriptions of diseases and disease processes, the author has devoted chapters to general problems in therapy, nutritional diseases, vitamin deficiencies, endocrine diseases, and special procedures. Also, diet lists, which have always been a source of worry to the general practitioner, are included.

The author's treatment of the viral, mycotic, protozoal, and metazoal infections and infestations in commendable at this time, because of their importance to physicians in the armed forces and to civilian doctors after the concluson of hostilities.

In presenting this text as a manual, or for reference, the author shows himself undoubtedly an authority.

JACK I. FEINMAN.

Glue and Gelatine. By Paul I. Smith. 145 pages, including index. Chemical Publishing Co., Inc., Brooklyn, N. Y.

The author of this book is undoubtedly a leather chemist in England, since his knowledge of gelatin, at least, is about two decades behind current practice in this country. In the United States the gelatin and glue industries long since have parted company, and it is almost considered poor taste by gelatin chemists to mention the two in the same sentence. One cannot get a clear picture of gelatin

chemistry, manufacture or use from a perusal of this book. It was probably a somewhat too optimistic approach by the author even to attempt it in 145 pages.

There is a long list of deficiencies in this text. No modern work on gelatin can fail to present the effect of the treatment given a precursor on the physico-chemical properties of the resultant gelatin. It has long been established that the variation in the isoelectric point is one of the most important effects of such differences in treatment and yet the author does not discuss this.

The Bloom gelometer is the standard apparatus for measuring jelly-strength, but it is only briefly mentioned in passing. The manufacturing technic described is not on a level with that used here and it is doubtful if a really high-grade product, by our standards, could be achieved by it.

The author in discussing uses illustrates the old block and frame technic for producing gelatin capsules, which is, even in England, almost replaced by the rotary-die method, an American development of some ten years ago.

For the purpose intended this book is hardly a commendable achievement.

L. F. Tice.

Road to tomorrow...

ENDLESS is the road of pharmaceutical achievement — reaching down to the dawn of medicine—winding up and up to greater discoveries yet to come.

Many milestones along this never-ending Road have been firmly placed by painstaking research performed in laboratories of Parke, Davis & Company. ADRENALIN*, PITUITRIN*, ANTUITRIN-S*, SYNAPOIDIN*, THEELIN, MAPHARSEN*, ESCHATIN*, DILANTIN* SODIUM . . . all are keen-edged weapons in the arsenal of modern therapeutics . . . all are on the shelves of every truly professional pharmacy in the land . . . all are Parke-Davis milestones along the Road to Tomorrow.

The Never-Ceasing Journey

Parke-Davis stands solidly upon a foundation of more than three-quarters of a century of pharmaceutical progress. During those years scientists at Parke-Davis evolved strict principles of drug standardization for uniform potency. They introduced to pharmacy and medicine vital plant drugs, biologicals, chemotherapeutic agents, endocrines, vitamins and other prescription preparations.

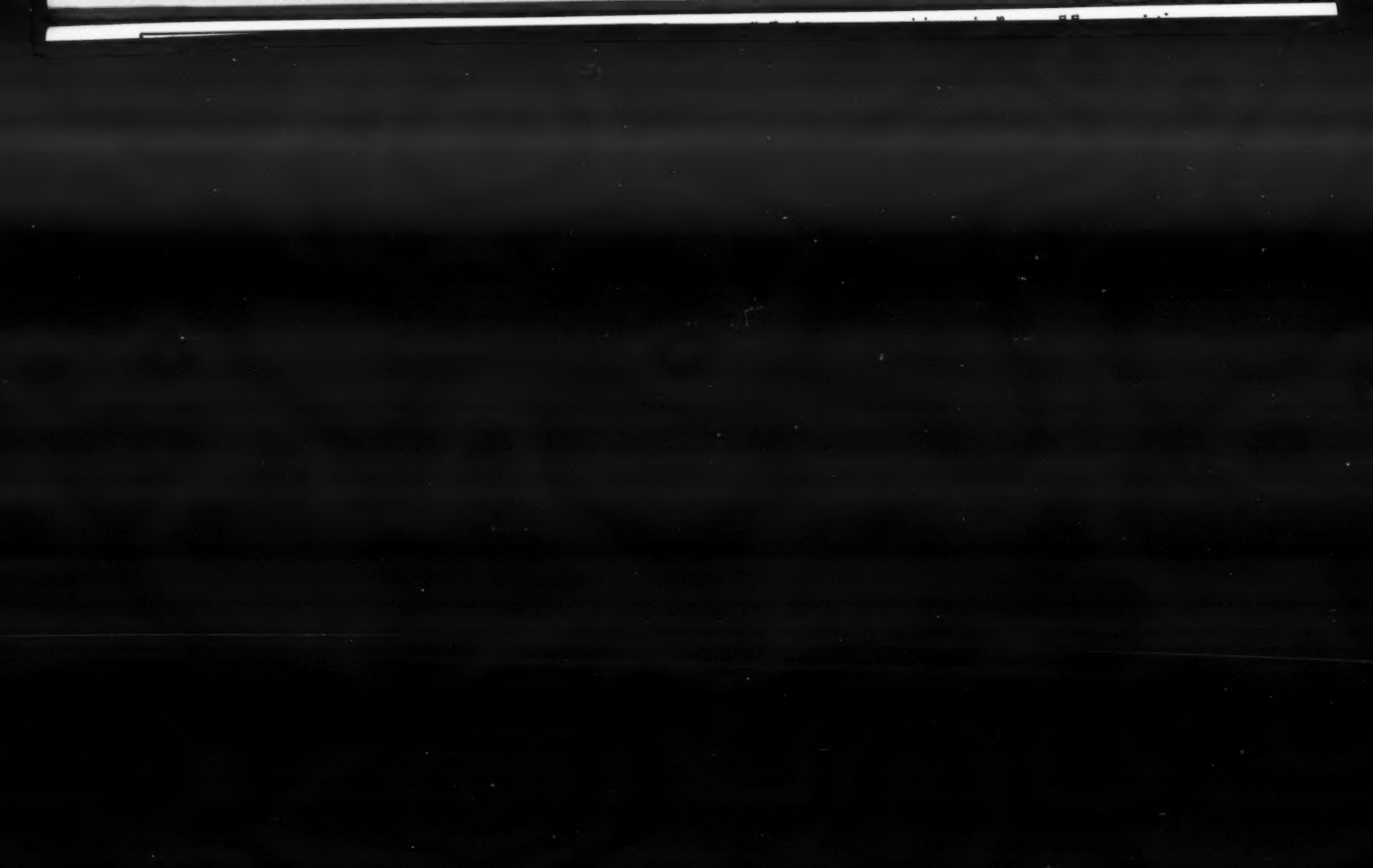
Parke-Davis research men still march down the endless road . . . Today it is the isolation of a new vitamin . . . Tomorrow—who knows? Through their skill drugs will be made safer—more effective. They will continue to supply world-wide Pharmacy and Medicine with products that are always . . . MEDICAMENTA VERA.

*Trade-marks Reg. U. S. Pat. Off.

ARMY E NAVY

PARKE, DAVIS & COMPANY

DETROIT, MICHIGAN



American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

Former Editors of the Journal have been: Daniel B. Smith, 1825-1828; Benjamin Ellis, 1829-1831; Robert E. Griffith, 1831-1836; Joseph Carson, 1836-1850; William Procter, Jr., 1850-1871; John M. Maisch, 1871-1893; Henry Trimble, 1893-1898; Henry Kraemer, 1898-1917; George M. Beringer, 1917-1921, and Ivor Griffith, 1921-1941.

Established and maintained as a record of the progress of pharmacy and the allied sciences, the Journal's contents and policies are governed by an Editor and a Committee on Publications elected by the members of the College.

Manuscripts should be sent to the Editor, who does not assume any responsibility in connection with the views or investigations of contributors of accepted manuscripts, other than to exercise general care in selection.

Contributors are allowed a reasonable number of copies of this Journal, free of charge, if applied for when the proof is returned.

Reprints, if desired, should be ordered when the proof is returned. The table below shows the *approximate* cost of reprints, the make-up of the pages to be identically the same as in the Journal. The actual cost may vary from the figures given, and will depend upon the amount of presswork, paper, binding, and other factors. Reprints containing half-tones may be expected to cost somewhat more than the rates given.

	2 pp.	4 pp.	8 pp.	16 pp.	Covers with Titles
50 copies.....	$3.50	$6.00	$10.50	$11.25	50 copies $5.00
100 "	4.25	7.00	14.00	15.00	100 " 6.50
250 "	5.25	9.00	18.75	20.00	250 " 10.25